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09/477,962	01/05/2000	BEN SHEN	2500.125US2	9979

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Law Offices of Jonathan Alan Quine
P O Box 458
Alameda, CA 94501

EXAMINER

KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 09/17/2003

27

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/477,962

Applicant(s)

SHEN ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 9, 10, 12-14, 21, 40-45, 71 and 73 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 9, 10 and 12-14 is/are allowed.
- 6) ☒ Claim(s) 1-3, 21, 40-45, 71 and 73 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Application Status

1. In response to the previous Office action on the merits, a Final rejection (Paper No. 17, mailed on December 14, 2003), Applicants filed an after-final amendment received on May 9, 2003 (Paper No. 22) and a RCE with an amendment received on July 3, 2003 (Paper No. 26); the amendments in Paper No. 22 are equivalent to Paper No. 26. Said amendment cancelled Claims 5, 15, 17, and 72 and amended Claims 1, 10, 12-14, 21, 40, 71, and 73. Thus, Claims 1-3, 9, 10, 12-14, 21, 40-45, 71, and 73 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/115,435 filed on January 6, 1999 and 60/118,848 filed on February 5, 1999.

U.S. Provisional application 60/115,435 does not contain any sequence information, thus, Claims 1-3, 9, 10, 12, 13, 14, 21, 40-45, 71, and 73 do not have support dating back to this earliest date. U.S. Provisional application 60/118,848 does contain some sequence information relative to SEQ ID NO:115 (the polypeptide) and SEQ ID NO:1 (57583-58854bp) (the encoding nucleotide sequence), but does not have sequence information relative to at least SEQ ID NOs: 109, 99, 96, 100, and 97. Thus the following are priority dates for the subject matter for each of the pending claims:

60/118,848 (February 5, 1999)

Claims 1, 9, 10, 21, 71, and 73

instant application (January 5, 2000)

Claims 2, 3, 12-14, and 40-45

Drawings

3. The drawings filed on July 3, 2003 (Paper No. 25) are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required in response to the instant Office action and may not be held in abeyance (see 37 C.F.R. § 1.85(a)).

Withdrawn - Objections to the Specification

4. Previous objection to the specification for being confusing is withdrawn by virtue of Applicants' amendments to the specification. The Examiner notes that support for the inclusion of accession number "AAD07904" for RfaE is found in the originally filed specification considering that "AA07904" was a typographical error as originally filed.

The Examiner also notes that the position numbers with respect to DNA sequence in Table II have been deleted to avoid the confusion noted by the Examiner. Applicants describe these numbers as "unnecessary and unhelpful" since the Sequence Listing lists the open reading frames separately. The Examiner disagrees that the encoding DNA, from bp-to-bp, would be unhelpful because only the encoded ORFs, that is the amino acid sequences, are separately listed in the sequence listing. However, as written, the specification is clear. The Examiner notes that SEQ ID NOs: 1 and 2, taken together, constitute all the encoding DNA disclosed in the instant application; particular proteins that are encoded are found in SEQ ID NOs: 93-126.

Withdrawn - Claim Objections

5. Previous objection to Claims 21, 40-45, and 71-73 for containing non-elected subject matter is withdrawn by virtue of Applicants' amendment.

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6. Previous objection to Claim 5 for having a period embedded within the text is withdrawn by virtue of Applicant's cancellation of said claim.

7. Previous objection to Claims 12-15 for containing references to orfs using terms like "blmVIII" instead of the SEQ ID NOs as used throughout the rest of the claims is withdrawn by virtue of Applicants' amendment and/or cancellation of said claims.

8. Previous objection to Claim 73 for having a typographical error is withdrawn by virtue of Applicant's amendment.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

9. Previous rejection of Claims 40-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of "a nucleic acid" is withdrawn by virtue of Applicants' amendment.

10. Previous rejection of Claim 72 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "a resistance gene from the bleomycin gene cluster" is withdrawn by virtue of Applicants' cancellation of said claim.

11. Previous rejection of Claims 5 and 10 and 40-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing the language of Claims 5 and 10 is withdrawn by virtue of Applicants' cancellation and/or amendment.

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12. Previous rejection of Claims 17 and 40-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the added limitation of encoding a module is withdrawn by virtue of Applicants' cancellation and/or amendment.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

13. Previous rejection of Claims 1-3 and 40-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "stringent conditions" is maintained although Applicants have amended the claims to read "highly stringent". The metes and bounds of the term "highly stringent" are also unclear. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the term "highly stringent" is clear with respect to its metes and bounds based on the disclosure, particularly page 10, line 33 to page 11, line 2. The Examiner disagrees. The specification describes general high stringency hybridization conditions with terms like "about" and using a T_m as a reference. Firstly, these limitations cannot be read into the claims. Secondly, the limitations in the specification are unclear. Hybridization conditions include, at a minimum, wash conditions to define how similar the sequences must be to remain hybridized. Such conditions, at a minimum, include a defined salt concentration and a defined temperature. Without such definite conditions, the term "highly stringent" is unclear.

14. Previous rejection of Claims 21 and 40-45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "a bleomycin" of "a bleomycin analogue" is maintained. Claims 71 and 73 are added to this rejection. Thus, Claims 21, 40-45, 71, and 73 are rejected under 35

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U.S.C. § 112, second paragraph, as being indefinite for the term “a bleomycin” of “a bleomycin analogue”. Applicants’ arguments have been fully considered but are not deemed persuasive.

Applicants argue that “a bleomycin is a compound that belongs to the family of bleomycins, and a bleomycin analogue is an analogue of a member of the bleomycin family.” The Examiner fails to see how this argument clarifies the definition. If the Examiner assumes that “a bleomycin” indicates a family of compounds, the structural components of such compounds are wholly undefined by the specification. Only a description of “isolated by Umezawa in 1996” is found; not even a reference is noted. Thus, the metes and bounds of the structures of the family of bleomycins are wholly unclear. Additionally, Applicants have still not answered the questions “Is the analogue a structural analogue? a functional analogue?” as previously posed. Applicants merely again cite that the term is found in other patent claims. Again, the Examiner reiterates, “Without a complete understanding of the claims and the specification, which can define the term, this argument is not persuasive” since all patent claims take their definition from the specification and the state of the art. For all these reasons, the instant rejection is maintained.

15. (New) Claims 71 and 73 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term “bleomycin gene cluster” is unclear as to its metes and bounds as based on the specification. A single example of a bleomycin gene cluster is defined by SEQ ID NOs: 1 and 2. Is the entirety of these two SEQ ID NOs included in the gene cluster? If not, what portion(s) are necessary. As noted above, the term “bleomycin” is also unclear so a functional definition is, thus, unclear as well.

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New or Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

16. Previous rejection of Claims 1-3, 21, 40-45, and 71-73 are rejected under 35 U.S.C. § 112, first paragraph, written description, is maintained and amended as set forth below. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that examples of an isolated bleomycin gene cluster has been provided; the Examiner agrees that a *single* example of a bleomycin gene cluster has been provided. The specification does not provide one of skill in the art the tools to recognize other gene clusters that produce bleomycin that is particular structural requirements of such a cluster. Applicants argue that modification to the gene cluster have also been provided, wherein the gene cluster produces enzymes that produce different bleomycins. The Examiner notes, however, that a minimal bleomycin gene cluster has not been provided, i.e., what portions of the entirety of SEQ ID NOs: 1 and 2 is required to make a bleomycin. For all these reasons, Applicants arguments are not persuasive since one of skill in the art would be unable to recognize bleomycin gene clusters other than the single example provide, i.e., a representative number of species has not been provided along with a structure/function correlation of species of the claimed genus.

(New Issue) For Claims 1-3, the variable structure of "highly stringent" coupled with the vague functionality of "oxidase activity" is insufficient to satisfy the requirements of written description. The instant specification describes SEQ ID NO:115 as an oxygen-independent coproporphyrinogen III oxidase and has adequate written description for any DNA encoding SEQ ID NO:115. Even if the term "highly stringent" were clear enough to define the structural variability of the instant claims, the vague function of "oxidase activity" is insufficient to satisfy

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written description. The specification has not described nucleic acid sequence encoding, for example, glucose oxidase, having the structural limitations defined in the claim. Thus, the activity must be specific to that which is described in the specification, namely, having oxygen-independent coproporphyrinogen III oxidase activity.

17. (New) Claim 71 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for cells with modified bleomycin gene clusters wherein the blmA and/or blmB genes are overexpressed to produce elevated bleomycin levels, does not reasonably provide enablement for cells with modified bleomycin gene clusters wherein the other bleomycin genes are overexpressed or otherwise modified to produce elevated bleomycin levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

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experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification provides examples of elevated bleomycin levels with the overexpression of blmA and/or blmB; their overexpression for the production of more bleomycin can be easily understood knowing their roles as encoding resistance proteins (more resistance proteins means the cell can produce more bleomycin without killing itself). No other examples of increasing bleomycin production are described. Numerous genes in the cluster could be modified and possibly produce higher (or lower) levels of bleomycin. No direction or guidance in the identification of such genes is provided. The state of the prior art is vast with respect to polyketide synthases, but the bleomycin gene cluster is somewhat of a hybrid synthase gene cluster, thus, its unpredictability upon mutation is very high. For these reasons, the full scope of the instant claim is not enabled.

Maintained - Claim Rejections - 35 U.S.C. § 102

18. Previous rejection of Claims 1, 40, 41, and 43-45 under 35 U.S.C. § 102(b) as being anticipated by Redenbach *et al.* is maintained as set forth below. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that it has not been *prima facie* established that the Redenbach *et al.* DNA encodes an oxidase as required by the limitation of the claims requiring the nucleic acid encode an oxidase. The Examiner disagrees since both the sequence and the activity of the

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encoded protein are inherent features of the DNA taught by Redenbach *et al.* Redenbach *et al.* teach the nucleotide sequence as encoding an oxygen-independent coproporphyrinogen III oxidase as evidenced by GenBank Accession Number AL136503 (see pages 11-12 of print-out for Applicants' convenience), which is the related accession number to the non-patent literature publication of Redenbach *et al.*

Applicants argue that the GenBank reference, used as support for the oxidase activity of the particular portion of the C77 cosmid with similarity to a DNA encoding SEQ ID NO:115, does not antedate the filing date of the instant application. However, both the sequence and the described activity are inherent features of the cosmid taught by Redenbach *et al.* and "[i]n certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. In re Wilson, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism" (see M.P.E.P. § 2124).

Applicants also argue that Redenbach *et al.* does not teach a nucleic acid within the limitations of hybridizing under highly stringent conditions. However, this term is unclear as noted above.

Summary of Pending Issues

19. The following is a summary of the issues pending in the instant application. All must be addressed in a complete response to the instant Office action:

- a) Drawings are informal
- b) Claims 1-3 and 40-45 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "stringent conditions".
- c) Claims 21 and 40-45 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "a bleomycin" of "a bleomycin analogue".

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- d) Claims 71 and 73 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for the term "bleomycin gene cluster".
- e) Claims 1-3, 21, 40-45, and 71-73 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
- f) Claim 71 stands rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.
- g) Claims 1, 40, 41, and 43-45 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Redenbach *et al.*

Conclusion

20. Claims 9, 10, and 12-14 are allowed; Claims 1-3, 21, 40-45, 71, and 73 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



KMK

September 16, 2003